DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Dr. James Pan, PharmD
Associate Director, Regulatory Affairs
Forest Laboratories, Inc.
Harborside Financial Center Plaza V, Suite 1900
Jersey City, NJ 07311

RE: NDA # 022522
Daliresp® (roflumilast) tablets
MA # 64

Dear Dr. Pan:

This letter notifies Forest Laboratories, Inc. (Forest) that the Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has become aware of oral statements made by Forest sales representatives on October 12, 2011, to a healthcare professional, regarding its drug Daliresp® (roflumilast) tablets (Daliresp), that were submitted as a complaint to the OPDP Bad Ad Program. The sales representatives' statements are false or misleading because they broaden the indication and minimize serious risks for Daliresp. Thus, this promotional activity misbrands Daliresp in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(f)(1), (n).

Background

Below are the indication, limitations of use, and summary of the most serious and most common risks associated with the use of Daliresp.[1]

According to its FDA-approved product labeling (PI):

> Daliresp® is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.
>
> *Limitations of Use*
> Daliresp is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

Daliresp is also associated with serious risks, as reflected in its PI. Specifically, Daliresp is contraindicated in patients with moderate to severe liver impairment. The PI for Daliresp also contains Warnings and Precautions regarding psychiatric events including suicidality, weight

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional activity cited in this letter.

decrease, and important drug interactions. The most common adverse reactions are diarrhea, weight decrease, nausea, headache, back pain, influenza, insomnia, dizziness, and decreased appetite.

Prior Communications with OPDP

OPDP is concerned that the violative conduct described above occurred despite Forest's September 15, 2010, Corporate Integrity Agreement (CIA) with the Office of Inspector General of the Department of Health and Human Services that requires Forest to ensure that its Policies and Procedures address "appropriate ways to conduct Promotional . . . Functions in compliance with all applicable FDA requirements" [III(B)(3)(c)], and to provide specific training to its employees engaged in Promotional Functions on "all applicable FDA requirements relating to Promotional . . . Related Functions . . . ." [III(C)(2)(b)].

False and misleading statements from Forest sales representatives are particularly troubling considering OPDP expressed concerns regarding similar violative promotional activities as recently as April 2011. On April 28, 2011, OPDP sent Forest an untitled letter for Savella (milnacipran HCL) Tablets (Savella). The letter concerned statements made by a Forest sales representative which promoted unapproved uses for Savella and minimized the serious risks associated with Savella.

Furthermore, in letters dated May 13, 2011, and July 22, 2011, OPDP provided advisory comments to Forest regarding proposed launch promotional materials specifically for Daliresp. Among other concerns, OPDP recommended that Forest remove claims that implied that Daliresp is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. OPDP is concerned that Forest is continuing to promote its prescription products in a violative manner despite clear direction from OPDP.

Broadening of Indication

On Wednesday, October 12, 2011, two sales representatives from Forest made a sales call to a physician's office. During this sales call, the sales representatives stated in word or substance that Daliresp was effective for COPD exacerbations. However, neither sales representative presented the appropriate patient population for Daliresp as described in the approved indication, i.e., patients with severe COPD associated with chronic bronchitis and a history of exacerbations. In addition, the sales representatives did not present Daliresp's Limitations of Use. Specifically, they did not discuss that Daliresp is not a bronchodilator and is not indicated for the relief of acute bronchospasm as described in the INDICATIONS AND USAGE and WARNINGS AND PRECAUTIONS sections of the PI. Therefore, the sales representatives' oral statements misleadingly broaden the indication for Daliresp by suggesting that the drug is safe and effective in a broader range of conditions and patients than has been demonstrated by substantial evidence or substantial clinical experience.

Minimization of Risk

During the October 12, 2011, sales call, the sales representatives minimized serious risks associated with Daliresp. Specifically, while the sales representatives responded to direct

questions regarding the risks of weight loss and psychiatric events including suicidality in a manner which is consistent with the WARNINGS AND PRECAUTIONS section of the PI, these risks were immediately downplayed with anecdotal claims regarding other physicians who have prescribed the drug, were pleased with it, and were not reporting **any** adverse events. Furthermore, the sales representatives minimized the risk of weight loss by indicating that this adverse reaction may actually be beneficial in COPD patients who are overweight. In direct contrast, the WARNINGS AND PRECAUTIONS section of the PI states, "If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and **discontinuation of DALIRESP should be considered**." (emphasis added)

The overall impression created by this presentation minimizes the serious risks associated with Daliresp and suggests that the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Conclusion and Requested Action

For the reasons discussed above, the oral statements made by the Forest representatives misbrand Daliresp in violation of the FD&C Act, 21 U.S.C. 352(f)(1), (n).

OPDP requests that Forest immediately cease violative promotional activities and the dissemination of violative promotional materials for Daliresp such as those described above. Please submit a written response to this letter on or before August 16, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Daliresp that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Drug Promotion (DPDP) and the Division of Consumer Drug Promotion (DCDP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to MA # 64 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Daliresp comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Roberta Szydlo, R.Ph.
Regulatory Review Officer
Division of Professional Drug Promotion
Office of Prescription Drug Promotion

{See appended electronic signature page}

Lisa Hubbard, R.Ph.
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/s/

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08/01/2012

LISA M HUBBARD
08/01/2012